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A CASE-CONTROL STUDY OF BREAST CANCER STRATIFIED BY ESTROGEN RECEPTOR STATUS

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A population-based case-control study was conducted to examine whether tumor estrogen receptor status differentiated risk factor patterns for breast cancer. From December 1980 to December 1982, 458 women with newly diagnosed breast cancer and 568 control women, aged 20–54 years, from the Atlanta, Georgia, metropolitan area were interviewed. On the basis of tumor estrogen receptor results, cases were classified as receptor-positive or receptor-negative. Intercase analysis showed that age was positively and significantly associated with estrogen receptor-positive breast cancer ($p = 0.001$); the relative risk for an estrogen receptor-positive as opposed to an estrogen receptor-negative tumor was elevated threefold among women aged 50–54 years compared with those aged <35 years. In the case-control analysis, race was the only individual factor that demonstrated a significant difference in the risk for estrogen receptor-positive versus estrogen receptor-negative cancer ($p < 0.05$), with blacks being at a 25% excess risk for estrogen receptor-negative cancer compared with whites. Although a history of benign breast disease was a risk factor for both positive and negative tumors, the association was stronger for the estrogen receptor-positive tumors. Postmenopausal women were at a lower risk for both cancer subtypes compared with premenopausal women. Compared with nonusers, women who had ever taken oral contraceptives had a 16% decrease in the risk for receptor-positive cancer and a 22% increase in the risk for receptor-negative cancer. These results are consistent with the notion that certain exposure variables may relate to hormonal status, possibly by augmentation or suppression of estrogen receptor activity.

breast neoplasms; receptors, estrogen

Epidemiologic studies and clinical research support a role for estrogens in the etiology of breast cancer (1–3), yet the underlying mechanisms have not been eluci-

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dated. In order for estrogen to influence the biologic activity and growth rate of a target cell population, such as breast tissue, specific estrogen receptor proteins, termed estrophilin, must be present (4, 5). Estrogen receptors are responsible for mediating estrogenic effects on target cell genes. Israel and Band (6) hypothesized that activation of the gene coding for estrophilin and expression of receptor protein in breast tumor tissue are part of the process of neoplastic transformation. Thus, the study of estrogen receptor status may provide insight into how hormones act in the carcinogenic process.

Approximately two thirds of breast cancers contain measurable levels of estrophilin (5, 7). The presence (ER+) or absence (ER−) of receptor protein is an important prognostic factor, with estrogen receptor positivity associated with improved response to hormonal therapy, lower recurrence rates, and longer survival compared with estrogen receptor-negative cancer (5, 7–10). To date, little attention has focused on whether estrogen receptor status is also related to etiologic factors. If estrogen receptor status depends upon specific risk factors, receptor-positive and receptor-negative tumors may result from separate pathogenic processes. The present study was undertaken to determine whether estrogen receptor-positive and estrogen receptor-negative breast cancer have different risk factor profiles.

Materials and Methods

Data were obtained from participants in the Atlanta, Georgia, component of the Cancer and Steroid Hormone Study conducted by the Centers for Disease Control. A detailed review of the methodology of this study has been published elsewhere (11). In brief, all newly diagnosed, histologically confirmed cases of breast cancer among women 20–54 years of age who were residents of the metropolitan Atlanta area and were diagnosed between December 1980 and December 1982 were identified. Of the 659 cases ascertained, interviews were completed on 561 (85 per cent). Nonparticipation was due to patient refusals (2 per cent), physician refusals (6 per cent), illness (3 per cent), changes in residence (1 per cent), death (1 per cent), and other reasons (2 per cent). Hospital abstracts and pathology reports provided information about tumor characteristics. The present analysis was limited to cases with both interview and unequivocal tumor estrogen receptor data ($n = 458$) and therefore excluded women with missing tumor estrogen receptor data ($n = 86$) or equivocal estrogen receptor assay results ($n = 15$). Two women with multiple primary breast cancers also were excluded.

The control group consisted of women without breast cancer, 20–54 years of age, from the same geographic area as the cases, who agreed to an interview after selection by random-digit telephone dialing (12). Controls were frequency-matched to the cases by five-year age group. Of the 629 women selected as controls, 90 per cent ($n = 568$) participated, 6 per cent refused, and 4 per cent were not interviewed for a variety of other reasons. The overall two-stage random-digit dialing response rate for controls was 80 per cent.

Trained interviewers administered standardized personal interviews to all study subjects, obtaining detailed information on reproductive history, menstrual history, use of exogenous hormones, family history of breast cancer, previous benign breast disease, and sociodemographic variables. Memory aids (a book of photographs of hormone preparations and a detailed life-events calendar) were used to elicit accurate past exposure information. Menopausal status was determined by reported time since last menstrual period. Women were considered postmenopausal if they had not had a menstrual period for more than six months, and they were classified according to the reasons for menstrual ces-

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sation; surgically menopausal women were further classified according to their ovarian status.

Estrogen receptor information, including whether the tumor was positive or negative, as well as the level of receptor protein, was abstracted from the laboratory and pathology reports of each case. A laboratory questionnaire, completed by each of the six laboratories that performed receptor assays on tumors from the present case series, documented estrogen receptor assay methods and procedures; the definition of positive, borderline, and negative test results was recorded, and each case's result was interpreted accordingly. Two thirds of the tumor specimens were assayed at the same laboratory, and 98 per cent of the samples were assayed by the standard dextran-coated charcoal method (4). The proportions of positive and negative tumors were similar across laboratories.

Data analysis was performed with both intercase (estrogen receptor-positive compared with estrogen receptor-negative breast cancer cases) and case-control (cases stratified by receptor status compared with the same group of controls) approaches. The measure of association used was the relative risk (RR), as estimated by the odds ratio (13). Stratified techniques were utilized to adjust for the effects of confounding variables (14), deriving adjusted maximum likelihood odds ratio estimates (15). For the adjusted relative risks, approximate 95 per cent confidence intervals (CI) were calculated (16). For exposure patterns, statistical significance was assessed by Mantel's test for linear trend (17). To control for the effects of multiple potential confounding factors, polychotomous logistic regression was performed, permitting modeling of estrogen receptor-positive case, estrogen receptor-negative case, or control status as the main classification (dependent) variable (18, 19). This procedure allowed estimation of the subgroup-specific risk parameters and direct statistical significance testing of differences between receptor-positive versus receptor-negative breast cancer cases compared with controls.

Results

A total of 44.5 per cent of the 458 breast tumors were estrogen receptor-positive, while 55.5 per cent were estrogen receptor-negative. Cases with estrophilin-positive cancer were about two years older, on average, than estrophilin-negative cases, the mean ages being 45.1 and 42.7 years, respectively ($p = 0.003$). The lower proportion of receptor-positive breast cancer in this study compared with previous reports probably reflects the younger age distribution of women in the current study. Because cases were not age-matched, intercase comparisons enabled an assessment of the relationship between age and receptor status. The relative risk for developing estrogen receptor-positive versus estrogen receptor-negative breast cancer increased directly with age ($p = 0.001$) (table 1). The risk for an estrophilin-positive tumor, as opposed to an estrophilin-negative tumor, was 2.9 among women 50–54 years compared with those less than 35 years. Black women had a lower risk for estrogen receptor-positive breast cancer compared with white women. An examination of sociodemographic factors showed that there were no differences between case groups according to education, income, or marital status, controlling for age and race.

Further analyses pursued relationships by utilizing a case-control approach. The relative risks for estrogen receptor-positive and estrogen receptor-negative breast cancer by reproductive variables and menopausal status are presented in table 2. Nulliparous women were at slightly increased risk for both types of tumors. Number of livebirths was inversely related to the risk for an estrogen receptor-positive tumor ($p = 0.03$); results were similiar after adjustment for age at first livebirth (not shown). No consistent relationship was seen between number of livebirths and estrogen receptor-negative cancer. Although parity appeared to be a more important predictor of risk than age at first birth for receptor-positive cancer, women who were 29 years or older at first livebirth were at an in-

TABLE 1

Intercase relative risks (RR) with 95% confidence intervals (CI) for estrogen receptor-positive breast cancer, according to age at diagnosis and race, Atlanta, Georgia, 1980–1982*

Variable	ER+ cases		ER− cases		RR	95% CI
	n	%	*n*	%		
Age (years)						
<35	16	7.8	37	14.6	1.00	
35–39	29	14.2	51	20.1	1.32	0.6–3.0
40–44	38	18.6	55	21.7	1.59	0.7–3.5
45–49	54	26.5	58	22.8	2.15	1.0–4.6
50–54	67	32.8	53	20.9	2.92	1.4–6.2
χ_1 for trend					3.72 ($p = 0.001$)	
Race†						
White	169	82.8	182	72.2	1.00	
Black	35	17.2	70	27.8	0.59‡	0.4–1.0

*ER+ is estrogen receptor-positive cancer; ER− is estrogen receptor-negative cancer.
† Excludes other races (two ER− cases).
‡ Age-adjusted.

TABLE 2

Relative risks (RR) with 95% confidence intervals (CI) for breast cancer stratified by estrogen receptor status,† according to reproductive factors and menopausal status, Atlanta, Georgia, 1980–1982*

Variable	ER+ cases ($n = 204$)		ER− cases ($n = 254$)	
	RR	95% CI	RR	95% CI
Ever had a livebirth				
Yes	1.00		1.00	
No	1.21	0.8–1.9	1.09	0.7–1.7
No. of livebirths				
0	1.00		1.00	
1–2	0.96	0.6–1.6	0.94	0.6–1.5
3–4	0.68	0.4–1.2	0.80	0.5–1.3
≥5	0.45	0.2–1.0	1.00	0.5–1.9
χ_1 for trend	−1.92	($p = 0.03$)	−0.26	($p = 0.40$)
Age (years) at first livebirth‡				
<20	1.00		1.00	
20–28	1.18	0.7–1.9	0.96	0.6–1.5
≥29	1.21	0.5–2.8	1.68	0.8–3.7
χ_1 for trend	0.40	($p = 0.34$)	0.53	($p = 0.30$)
Menopausal status				
Premenopausal	1.00		1.00	
Natural postmenopausal	0.71	0.4–1.4	0.88	0.5–1.7
Surgical postmenopausal	0.69	0.5–1.1	0.82	0.6–1.2
Ovaries remaining				
1–2	0.68	0.4–1.1	0.93	0.6–1.4
0	0.76	0.4–1.5	0.62	0.3–1.2

* Relative risks are based on age-adjusted case-control comparisons.
† ER+ is estrogen receptor-positive cancer; ER− is estrogen receptor-negative cancer.
‡ Adjusted for number of livebirths; excludes nulliparous women.

creased risk for receptor-negative cancer compared with controls (RR = 1.7, 95 per cent CI 0.8–3.7). Although not shown, nulliparous women were at somewhat higher risk compared with women who had a first livebirth before age 20 (RR = 1.6 for receptor-positive tumors, and RR = 1.1 for receptor-negative tumors). The association of estrogen receptor status with menopausal status showed that women who had

experienced either natural or surgical menopause, regardless of oophorectomy status, demonstrated lower, although not statistically significant, risk for both receptor-positive and receptor-negative cancer compared with premenopausal women. Age at menopause was not related to receptor status. Risk profiles did not vary notably between case groups (compared with controls) according to age at menarche, breast feeding, history of miscarriage, or history of prior stillbirth.

Family history of breast cancer was a statistically significant risk factor for both estrogen receptor-positive and estrogen receptor-negative disease (table 3). Women whose mother or sister(s) had breast cancer had 2.5 times the risk for developing receptor-positive tumors and a 2.2-fold elevation in the risk for receptor-negative cancers. Some elevation in risk was also associated with having an affected second-degree relative, although the relative risks were only of the magnitude of 1.3–1.6. Family history stratified by menopausal status showed stronger effects among premenopausal women for both estrogen receptor-positive and estrogen receptor-negative cancer, although there was no difference by estrogen receptor status. A previous history of benign breast disease also was associated with increased risk for both types of cancer, but was statistically significant only for estrogen receptor-positive tumors (RR = 2.0, 95 per cent CI 1.3–3.2). Although oral contraceptive use was not associated with the risk for breast cancer, risk estimates by estrogen receptor status were in opposite directions. Compared with nonusers, women who had used oral contraceptives had an 18 per cent decrease in the risk for receptor-positive cancer but a 22 per cent increase in the risk for receptor-negative cancer. Further evaluation of oral contraceptive use by duration revealed no consistent pattern for receptor-positive cancer; however, compared with nonusers, women who had taken oral contraceptives for six or more years had a 70 per cent increase in the risk for receptor-negative cancer. No substantial variations in risk patterns were noted according to the use of other exogenous hormones or history of smoking.

When indices of body size were considered, the risk for breast cancer stratified by estrogen receptor status did not vary consistently with height or weight (table 4), although those in the highest weight category (≥72 kg) were at the highest risk for both estrogen receptor-positive and estrogen receptor-negative tumors. There was, however, a direct increase in the risk for estrogen receptor-negative cancer according to Quetelet index ($p = 0.03$). Women

TABLE 3

Relative risks (RR) with 95% confidence intervals (CI) for breast cancer stratified by estrogen receptor status,† according to family history of breast cancer, prior breast disease, exogenous hormone use, and smoking, Atlanta, Georgia, 1980–1982*

Variable	ER+ cases ($n = 204$)		ER− cases ($n = 254$)	
	RR	95% CI	RR	95% CI
Family history of breast cancer				
First-degree relative	2.52	1.3–4.7	2.18	1.2–4.0
Second-degree relative	1.56	1.0–2.4	1.34	0.9–2.0
Previous benign breast disease	2.03	1.3–3.2	1.43	0.9–2.3
Ever used oral contraceptives	0.82	0.6–1.2	1.22	0.9–1.7
Ever used estrogen or other female hormones	0.98	0.7–1.4	0.97	0.7–1.3
Ever used topical estrogens	0.95	0.5–1.7	1.05	0.6–1.8
Ever smoked 100+ cigarettes	1.03	0.7–1.4	1.00	0.7–1.4

* Relative risks are based on age-adjusted case-control comparisons.

† ER+ is estrogen receptor-positive cancer; ER− is estrogen receptor-negative cancer.

with a Quetelet index of ≥25 experienced the highest risk for both types of tumors.

Finally, case-control multivariate analysis was performed to adjust simultaneously for several risk factors; variables that were predictors of breast cancer risk and differed according to estrogen receptor status were considered in deriving the final model. As shown in table 5, black women were at a lower risk for estrogen receptor-positive (RR = 0.7, 95 per cent CI 0.5–1.2) and higher risk for estrogen receptor-negative (RR = 1.3, 95 per cent CI 0.9–1.8) cancer than were whites, a difference that was statistically significant. Postmenopausal women experienced a lower risk for both tumor types compared with premenopausal women; the protective effect was greater for receptor-positive cancer (RR = 0.6, 95 per cent CI 0.4–0.9). A first-degree relative with breast cancer and history of benign breast disease conferred elevated risks for receptor-positive and receptor-negative disease; however, the associations were somewhat stronger for receptor-positive cancer. Directionally different risks were noted for the use of oral contraceptives, but risk estimates were not statistically significantly different. A Quetelet index of ≥25 was positively associated with both cancer subtypes.

Discussion

The risk factor profiles for estrogen receptor-positive versus estrogen receptor-negative breast cancer were dissimilar according to age and race. Age was positively and significantly associated with receptor-positive cancer, a finding that is consistent with other reports (20–22). It has been suggested that higher levels of circulating estrogens in young women may interfere with the measurement of estrogen-binding protein (23, 24), thereby accounting for the greater proportion of receptor-negative cancer among young compared with older women. More recently, investigators have proposed that lower levels of circulating

TABLE 4

Relative risks (RR) with 95% confidence intervals (CI) for breast cancer stratified by estrogen receptor status,† according to height, weight, and Quetelet index, Atlanta, Georgia, 1980–1982*

Variable	ER+ cases (n = 204)		ER− cases (n = 254)	
	RR	95% CI	RR	95% CI
Height (cm)				
≤159.9	1.00		1.00	
160.0–165.1	0.94	0.6–1.6	0.98	0.6–1.6
165.2–170.1	1.09	0.7–1.8	0.93	0.6–1.5
≥170.2	1.07	0.6–1.8	0.86	0.5–1.4
χ_1 for trend	0.46	(p = 0.32)	−0.72	(p = 0.24)
Weight (kg)				
<54.0	1.00		1.00	
54.0–58.4	0.66	0.4–1.1	1.15	0.7–1.9
58.5–62.9	1.25	0.8–2.1	1.23	0.8–2.0
63.0–71.9	1.09	0.7–1.8	1.09	0.7–1.8
≥72.0	1.29	0.7–2.3	1.72	1.0–2.9
χ_1 for trend	1.38	(p = 0.09)	1.63	(p = 0.05)
Quetelet index‡				
<20	1.00		1.00	
20–21	1.17	0.7–1.9	1.13	0.7–1.8
22–24	1.00	0.6–1.7	1.34	0.8–2.2
≥25	1.46	0.9–2.5	1.50	0.9–2.5
χ_1 for trend	1.21	(p = 0.11)	1.88	(p = 0.03)

* Relative risks are based on age-adjusted case-control comparisons.

† ER+ is estrogen receptor-positive cancer; ER− is estrogen receptor-negative cancer.

‡ Quetelet index: (weight in kilograms divided by height in centimeters squared) × 10,000.

TABLE 5

Multivariate relative risks† (RR) with 95% confidence intervals (CI) obtained from the polychotomous logistic regression analysis for the associations between selected variables and breast cancer stratified by estrogen receptor status,‡ Atlanta, Georgia, 1980–1982

Model§	ER+ cases		ER− cases		χ^2‖
	RR	95% CI	RR	95% CI	
Race					
White	1.00		1.00		
Black	0.74	0.47–1.16	1.25	0.85–1.83	4.09*
Menopausal status					
Premenopausal	1.00		1.00		
Postmenopausal	0.60	0.40–0.89	0.77	0.54–1.11	1.18
First-degree relative with breast cancer					
No	1.00		1.00		
Yes	2.28	1.23–4.21	2.05	1.13–3.74	0.10
History of benign breast disease					
No	1.00		1.00		
Yes	2.05	1.33–3.18	1.51	0.98–2.34	1.47
Ever used oral contraceptives					
No	1.00		1.00		
Yes	0.84	0.58–1.22	1.22	0.84–1.75	2.70
Quetelet index¶					
<20	1.00		1.00		
20–21	1.07	0.65–1.78	1.09	0.68–1.75	0.01
22–24	0.93	0.55–1.57	1.22	0.76–1.98	0.81
≥25	1.54	0.89–2.67	1.43	0.85–2.40	0.06

Model likelihood ratio $\chi^2 = 49.85$, 20 df ($p = 0.002$)

* $p < 0.05$.

† Relative risks are based on age-adjusted case-control comparisons.

‡ ER+ is estrogen receptor-positive cancer; ER− is estrogen receptor-negative cancer.

§ Each variable is simultaneously adjusted for all other variables.

‖ Test for the difference in beta coefficients for ER+ vs. ER− cases.

¶ Quetelet index: (weight in kilograms divided by height in centimeters squared) × 10,000.

progesterone in older, postmenopausal women may explain the age differences (5, 25), since progesterone limits the synthesis and activity of estrogen receptors (26, 27).

Although women who experienced either natural or surgical menopause, regardless of oophorectomy status, had a lower risk of disease compared with premenopausal women, menopausal status was not associated with estrogen receptor status. This finding contrasts with other studies which have shown a higher proportion of receptor-positive tumors among postmenopausal women (7, 22, 28, 29). This discrepancy may be due to differences in study populations, since the present study analyzed a series of women under 55 years of age and therefore did not include older postmenopausal women.

The finding that black women were at an increased risk for estrogen receptor-negative breast cancer compared with white women is consistent with previous reports (22, 30–32). Prior investigators (30–33) have speculated that younger age at diagnosis, more extensive disease at time of diagnosis, larger tumor size, poorly differentiated tumors, and a higher proportion of medullary tumors may account for the higher proportion of receptor-negative cancer among black compared with white breast cancer cases. In a study by Ownby et al. (34), no black-white difference was noted in estrogen receptor results, but

blacks had a higher prevalence of larger, higher grade tumors. In our data, the racial variance in estrogen receptor status persisted after adjustment for histologic type and extent of disease. Thus, it does not appear that differences in age or tumor characteristics explain the observed black-white differences in receptor status.

Apart from age and race, estrophilin-positive and estrophilin-negative breast cancer share most of the other risk factors, although the strength of the associations varied for the two disease subtypes. Several factors were somewhat stronger predictors of risk for estrogen receptor-positive cancer (family history, history of benign breast disease, premenopausal status, parity) or estrogen receptor-negative cancer (later age at first livebirth, long-duration oral contraceptive use), although differences in the relative risks were not significant.

Previous studies have not generally shown differences between estrogen receptor status and family history (20–22, 30). The present findings, together with other studies suggesting that family history exerts its effect through hormonal influences (35), provide some evidence in support of an etiologic role for elevated levels of endogenous estrogens (estrogen stimulates the synthesis of estrophilin), progesterone deficiency (progesterone inhibits estrophilin activity), and/or genetic predisposition which influences target tissue sensitivity to estrogen stimulation.

The finding that benign breast disease was a somewhat stronger risk factor for receptor-positive than receptor-negative tumors is consistent with one study (21) but contrasts with another (30). Differences in study results may be due to the specific subtypes of benign breast disease and/or the young age distribution of our study population. Some lesions, specifically fibroadenomas, are more likely to be estrophilin-positive and to occur among younger women than other benign lesions (9, 36). Further research is needed to correlate estrogen receptor activity in benign breast disease with subsequent risk of malignancy.

A number of other breast cancer risk factors that have been suggested to vary by estrogen receptor status were evaluated in this study. Similar to results from Hildreth et al. (21), estrophilin activity was related to parity. Nulliparous women were at somewhat increased risk for receptor-positive cancer, and risk was inversely related to the number of births, suggesting that the influence of parity on disease risk may be mediated through estrogen receptor activity.

Our results failed to confirm an association between estrogen receptor positivity and age at first livebirth or breast-feeding (21). In contrast, our data indicate that older age at first livebirth is linked to an elevation in risk for receptor-negative cancer. Additional studies of estrogen receptor status and reproductive risk variables are needed to examine whether different endocrine pathways may be operating in the development of estrophilin-positive versus estrophilin-negative cancer. Some of the discrepancy in findings may be due to the young age distribution of the present series of cases. Furthermore, since age at first livebirth was not a risk factor in this data set, it is difficult to interpret results of receptor status according to the timing of first birth.

The present findings were similar to previous observations (22, 37) that found that oral contraceptive users were less likely to have estrogen receptor-positive cancer. Hulka et al. (30) noted a nonsignificant decrease in median estrophilin levels for long duration (5+ years) of oral contraceptive use and markedly reduced median receptor values for preparations incorporating progestogens. Taken together, these findings are consistent with a slight protective effect of oral contraceptives against estrogen receptor-positive cancer. Biologically, this relationship may be mediated through progesterone's antagonistic effects on estrophilin activities. On the other hand, oral contraceptive use may have no direct influence on receptor-negative, hormone-independent, tumor growth. Our finding

that prolonged oral contraceptive use (6+ years) was associated with a 70 per cent increase in risk for receptor-negative cancer may represent a chance finding, and must await confirmation.

An elevation in the risk for estrogen receptor-negative cancer related to estrogen replacement therapy, as reported by Hildreth et al. (21), was not found in the present investigation. The present study, however, did not provide the optimal situation for evaluating menopausal estrogen use since the study population was truncated at the age of 54 years, resulting in a comparatively young group of postmenopausal women. The fact that obesity (Quetelet index) was found not to differ between case groups contrasts with some previous reports (38–40) that suggested a relationship between overweight and estrogen receptor-positive breast cancer. Finally, cigarette smoking was not associated with receptor status in this investigation, unlike the finding by Daniell (41) that smokers had a lower proportion of estrogen receptor-positive tumors. Case groups did not differ according to the number of cigarettes smoked per day or the duration of smoking (not shown). Lack of an association is noteworthy since smoking has been hypothesized to exert an antiestrogen effect, possibly through competitive binding of estrogen receptor sites (42).

Some consideration must be given to methodological limitations of the current study, primarily missing estrogen receptor data and validity of receptor information. Interviewed cases that did and did not have a tumor specimen submitted for estrophilin determination were no different with regard to age, race, menstrual status, and other risk factors; however, a higher proportion of women with missing receptor data had in situ cancer. This may be explained by the fact that specimens from biopsies and resections of in situ lesions may have been too small to submit for estrogen receptor determination. Studies have not consistently related receptor status to extent of disease (20, 36, 43). In the present study, since the number of cases excluded because of missing estrogen receptor status was small, overall results were probably not substantially affected.

Another limitation of this study was the lack of a universal standard for measuring estrophilin, which limits the ability to quantify the validity of estrogen receptor data. Precise estimates of sensitivity and specificity of test results could not be determined, yet it seemed reasonable to assume that misclassification of receptor status was not systematically related to age, race, or other risk factors included in this study. The net effect of such random misclassification would be to bias the risk estimates toward unity (44).

Although cautious interpretation of the findings in this study is warranted because of the possible operation of chance, it would appear that there are certain discriminators for risk of estrogen receptor-positive versus estrogen receptor-negative tumors. However, the extent to which these differences reflect effects associated with exposure(s), the disease process, or host influences remains to be elucidated.

Moolgavkar et al. (45) speculated that all malignant breast tumors are initially estrogen receptor-positive, but as the tumor undergoes clonal evolution and becomes more undifferentiated, the ability to express estrophilin is lost. If this is true, receptor status may reflect temporal changes in the biologic characteristics of the tumor as it progresses from a well differentiated to a poorly differentiated state. Estrogen receptor status could also reflect changes in host response and tumor aggressiveness, a concept consistent with previous observations that anaplastic, rapidly growing breast tumors are less likely to contain estrophilin (46–48).

On the other hand, it has not been established whether estrogen receptor-negative tumors represent an advanced stage of the disease or arise de novo (9, 49). Clinical studies have failed to demonstrate a rela-

tionship between extent of disease and receptor status (4, 20, 36, 43). It is possible that certain etiologic factors lead to the natural selection and growth of estrogen receptor-negative cells and that receptor negativity is an early, inherent characteristic of some breast cancers. This idea is supported by a recent study (50) which demonstrated that activation of an oncogene in vitro resulted in the selective growth of receptor-negative cells.

In summary, the major differences regarding risk factors for estrogen receptor-positive versus estrogen receptor-negative tumors were age and race. Although there was general consistency in the effects of other factors for the two tumor subtypes, the stronger effects of prior benign breast disease, premenopausal status, and parity on receptor-positive cancer risk are noteworthy, suggesting that certain hormonally related risk factors may predispose to the development of estrogen receptor-positive breast cancer. Although these findings are suggestive of dissimilarities between receptor-positive and receptor-negative cancers, further studies are needed to determine whether these patterns reflect separate pathogenetic mechanisms or different stages of a single pathway.

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